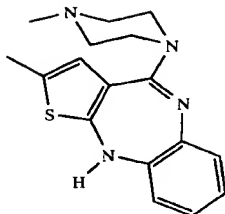


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-continued



In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical): 6 volumes
Intermediate 1: 75 g
N-Methylpiperazine (reagent): 6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent. A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120° C. and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until 2 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20° C. (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20° C. for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5° C. and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45° C. overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II olanzapine polymorph

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L). The mixture was heated to 76° C. and maintained at 76° C. for 30 minutes. The mixture was allowed to cool to 25° C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency $\geq 97\%$, total related substances $<0.5\%$ and an isolated yield of $>73\%$.

EXAMPLE 1

A portion of the hydroxypropyl cellulose was dissolved in 60 purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the olanzapine (1.18% w/w), ibuprofen (3% w/w), lactose (79.32% w/w) and a portion of the croscopovidone (5% 65 w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granu-

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lator. This mixture was then granulated with the hydroxypropyl cellulose solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. 5 The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the croscopovidone were added to the sized granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment. 10

Subcoating

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution. The operation was performed in a perforated coating pan.

Coating of Core Tablets

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension described above. The operation was performed in a perforated coating pan. 25

The coated tablets were lightly dusted with camauba wax and imprinted with appropriate identification.

We claim:

1. A composition for treating pain comprising olanzapine or a pharmaceutically acceptable salt or solvate thereof; and one or more Drug Useful in the Treatment of Pain in a weight ratio of from about one part olanzapine to from about one (1) part to about one thousand (1000) parts Drug Useful in the Treatment of Pain. 30

2. A composition of claim 1 wherein the Drug Useful in the Treatment of Pain is an NSAIDS.

3. A composition of claim 2 wherein the NSAIDS is selected from the group consisting of aspirin, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac or a pharmaceutically acceptable salt thereof. 40

4. A composition of claim 1 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing: 45

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828

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d
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007.

5. A composition of claim 4 wherein the Drug Useful in the Treatment of Pain is selected from the group consisting of aspirin, ibuprofen, and naproxen.

6. A composition of claim 1 wherein the weight ratio of olanzapine to Drug Useful in the Treatment of Pain is from about one part olanzapine to from about one (1) to about one hundred (100) parts Drug Useful in the Treatment of Pain.

7. A composition of claim 6 wherein the weight ratio is from about one part olanzapine to from about one (1) to about thirty (30) parts Drug Useful in the Treatment of Pain.

8. A composition of claim 7 wherein the weight ratio is from about one part olanzapine to from about one (1) to about ten (10) parts Drug Useful in the Treatment of Pain.

9. A composition of claim 8 wherein the Drug Useful in the Treatment of Pain is selected from the group consisting of morphine, acetaminophen, ibuprofen, and diclofenac.

10. A composition of claim 1 wherein the Drug Useful in the Treatment of Pain is an opioid compound.

11. A composition of claim 4 wherein the Drug Useful in the Treatment of Pain is an opioid compound.

12. A composition of claim 7 wherein the Drug Useful in the Treatment of Pain is an opioid compound.

13. A composition of claim 10 wherein the opioid compound is selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxycodone, buprenorphine, pentazocine, butorphanol, nabuphine, and buprenorphine.

14. A composition of claim 13 wherein the opioid compound is selected from the group consisting of morphine, oxycodone, hydromorphone, codeine, and methadone.

15. A composition of claim 1 wherein the Drug Useful in the Treatment of Pain is selected from the group consisting of Tylenol #3, tricyclic antidepressants (for example desipramine, imipramine, amitriptyline, nortriptyline), anti-convulsants (for example, carbamazepine, gabapentin, valproate), and serotonin reuptake inhibitors (for example, fluoxetine, paroxetine, citalopram, sertraline), mixed serotonin-norepinephrine reuptake inhibitors (for example venlafaxine, duloxetine), serotonin receptor agonists and antagonists, cholinergic (muscarinic and nicotinic) analgesics, and neurokinin antagonists.

16. A composition of claim 4 wherein the Drug Useful in the Treatment of Pain is selected from the group consisting of Tylenol #3, tricyclic antidepressants, anti-convulsants, and serotonin reuptake inhibitors, mixed serotonin-norepinephrine reuptake inhibitors analgesics, and neurokinin antagonists.

17. A composition of claim 16 wherein the Drug Useful in the Treatment of Pain is a tricyclic antidepressant.

18. A composition of claim 1 wherein the Drug Useful in the Treatment of Pain is an alpha adrenergic compound.

19. A composition of claim 18 central alpha-adrenergic active compound is Clonidine or a pharmaceutically acceptable salt thereof.

20. A composition of claim 4 wherein the Drug Useful in the Treatment of Pain is an alpha adrenergic compound.

21. A composition of claim 7 wherein the Drug Useful in the Treatment of Pain is an alpha adrenergic compound.

22. A composition of claim 1 wherein the composition can provide a synergistic analgesic effect.

23. A composition for treating pain comprising olanzapine, or a pharmaceutically acceptable salt or solvate thereof, and ibuprofen, or a pharmaceutically acceptable salt thereof, in a weight ratio of about one part olanzapine to from about one (1) to about one thousand (1000) parts ibuprofen.

24. A composition of claim 23 wherein the olanzapine is Form II olanzapine polymorph.

25. A composition of claim 23 wherein the weight ratio is about one part olanzapine to from about one (1) to about one hundred (100) parts ibuprofen.

26. A composition of claim 23 wherein the weight ratio is about one part olanzapine to from about one (1) to about thirty (30) parts ibuprofen.

27. A composition of claim 26 wherein the weight ratio is about one part olanzapine to from about one (1) to about ten (10) parts ibuprofen.

28. A method for treating pain comprising administering an analgesic dose of a composition comprising olanzapine or a pharmaceutically acceptable salt or solvate thereof; and one or more Drug Useful in the Treatment of Pain in a weight ratio of olanzapine to Drug Useful in the Treatment of Pain of from about one part olanzapine to from about one (1) to about one thousand (1000) parts Drug Useful in the Treatment of Pain.

29. A method of claim 28 wherein the Drug Useful in the Treatment of Pain is an NSAIDS.

30. A method of claim 28 wherein the weight ratio of olanzapine to Drug Useful in the Treatment of Pain is from about one (1) part olanzapine to from about one (1) to about one hundred (100) parts Drug Useful in the Treatment of Pain.

31. A method of claim 28 wherein the weight ratio of olanzapine to Drug Useful in the Treatment of Pain is from about one (1) part olanzapine to from about one (1) to about thirty (30) parts Drug Useful in the Treatment of Pain.

32. A method of claim 28 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366

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-continued

d
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007.

33. A method of claim 28 wherein the Drug Useful in the Treatment of Pain is selected from the group consisting of alpha adrenergic compounds and opioid compounds.

34. A method of claim 28 wherein the Drug Useful in the Treatment of Pain is selected from the group consisting of Tylenol #3, tricyclic antidepressants, anticonvulsants, and serotonin reuptake inhibitors, mixed serotonin-norepinephrine reuptake inhibitors analgesics, and neurokinin antagonists.

35. A method of claim 28 wherein pain is neuropathic pain.

36. A method of claim 28 wherein pain is nociceptive pain.

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37. A method of claim 28 wherein the pain is acute pain.

38. A method for treating pain comprising administering an analgesic dose of a composition comprising olanzapine, or a pharmaceutically acceptable salt or solvate thereof, and ibuprofen, or a pharmaceutically acceptable salt thereof, in a weight ratio of about one part olanzapine to from about one (1) to about one thousand (1000) parts ibuprofen.

39. A method of claim 38 wherein the olanzapine is Form II olanzapine polymorph.

40. A method of claim 38 wherein the weight ratio of olanzapine to ibuprofen is about one (1) part olanzapine to from about one (1) to about one hundred (100) parts ibuprofen.

41. A method of claim 40 wherein the weight ratio of olanzapine to ibuprofen is about one (1) part olanzapine to from about one (1) to about thirty (30) parts ibuprofen.

42. A method of claim 38 wherein the pain is neuropathic pain.

43. A method of claim 38 wherein the pain is nociceptive pain.

44. A method of claim 38 wherein the pain is acute pain.

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